JACC: HEART FAILURE VOL. 13, NO. 1, 2025
© 2025 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

REVIEW TOPIC OF THE MONTH

Diuretic Potentiation Strategies in Acute Heart Failure

Tariq Jamal Siddiqi, MD,[a] Milton Packer, MD,[b] Justin A. Ezekowitz, MBBCH, MSC,[c] Gregg C. Fonarow, MD,[d] Stephen J. Greene, MD,[e,f] Michelle Kittleson, MD,[g] Muhammad Shahzeb Khan, MD, MSC,[h,i,j] Robert J. Mentz, MD,[e,f] Jeffrey Testani, MD,[k,l] Adriaan A. Voors, MD,[m] Javed Butler, MD, MPH, MBA[n,o]

HIGHLIGHTS

- Guidelines recommend loop diuretic agents for AHF, but many patients are discharged with persistent congestion.
- All diuretic strategies have the potential to produce diuresis, but are accompanied by risk of acute increases in serum creatinine.
- Intensification of loop diuretic agents or adding vasopressin antagonists reduces body weight and improves dyspnea.
- Standardizing decongestion measurement and evaluating the long-term impact of diuretic strategies are essential.

ABSTRACT

Several trials have evaluated diuretic-based strategies to improve symptoms and outcomes in patients with acute heart failure (AHF). The authors sought to summarize the effect of different combination strategies on symptoms, physical signs, physiological variables, and outcomes in patients with AHF. Twelve trials were identified that assessed the addition of thiazide diuretics, sodium-glucose cotransporter 2 inhibitors, mineralocorticoid receptor antagonists, vasopressin receptor antagonists, carbonic anhydrase inhibitors, or loop diuretic intensification to conventional therapy for AHF. The trials evaluated short-term markers of congestion and symptoms, and none were powered for clinical outcomes. Short-term responses (such as relief from dyspnea, physical signs of congestion, and weight change) varied greatly across studies; all diuretic strategies were accompanied by short-term increases in serum creatinine and did not demonstrate benefits on mortality or recurrent heart failure events. The available evidence suggests that intensification of loop diuretic agents produces relief of physical signs of decongestion, but the importance of different strategies for short-term decongestion strategy for health status and long-term outcomes has not been established.
(JACC Heart Fail. 2025;13:14–27) © 2025 by the American College of Cardiology Foundation.

From the [a]Department of Internal Medicine, Baylor University Medical Center, Dallas, Texas, USA; [b]Baylor University Medical Center, Dallas, Texas, USA; Imperial College, London, United Kingdom; [c]Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada; [d]Division of Cardiology, University of California-Los Angeles, Los Angeles, California, USA; [e]Duke Clinical Research Institute, Durham, North Carolina, USA; [f]Division of Cardiology, Duke University School of Medicine, Durham, North Carolina, USA; [g]Department of Cardiology, Smidt Heart Institute, Los Angeles, California, USA; [h]Baylor College of Medicine, Temple, Texas, USA; [i]Baylor Scott and White Heart Hospital, Plano, Texas, USA; [j]Baylor Scott and White Research Institute, Baylor Scott and White Health, Dallas, Texas, USA; [k]Section of Cardiovascular Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA; [l]Baylor Scott and White Research Institute, Dallas, Texas, USA; [m]University of Groningen Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; [n]Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA; and the [o]Baylor Scott and White Research Institute, Baylor Scott and White Health, Dallas, Texas, USA.

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2024.09.017

SHOUT
SHARE
IT

Acute heart failure (AHF) is associated with significant morbidity, risk of rehospitalization, and mortality.[1] Guidelines recommend the use of loop diuretic agents to alleviate excess fluid, but many patients are discharged with persistent congestion.[2-7] Diuretics or drugs with diuretic properties, such as loop diuretic agents, carbonic anhydrase inhibitors, thiazide diuretics, sodium-glucose cotransporter 2 inhibitors (SGLT2is), vasopressin receptor antagonists, and mineralocorticoid antagonists, act on different parts of the nephron (**Central Illustration**). Loop diuretic agents are the cornerstone of diuresis and may be combined with other agents. We systematically review here the findings of clinical trials assessing the effects of adjunctive therapies on symptoms, physical signs of decongestion, kidney function, and outcomes in AHF.

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

HF = heart failure

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SGLT2i = sodium-glucose cotransporter 2 inhibitor

VAS = visual analog scale

METHODS

STUDY SELECTION AND DATA ABSTRACTION. All papers from the systematic search (Supplemental Table 1) were exported to EndNote reference library version X8.1 (Clarivate Analytics). Duplicates were sought and removed. Two independent reviewers (T.J.S. and J.B.) assessed the papers; only those that met the predefined criteria were selected, and a third investigator resolved discrepancies. Relevant papers were selected based on the title and abstract, after which the full text was read to confirm relevance. Only randomized clinical trials that compared diuretic potentiation strategies with placebo or control interventions in AHF were selected. Accordingly, trials including nondiuretic therapies (such as low-dose dopamine and nesiritide) and non-pharmacologic therapy (such as ultrafiltration) were excluded. In addition, we included only parallel-group, open-label, and double-blind trials in our analysis. Crossover trials were excluded. We also excluded observational data due to their inherent susceptibility to biases and confounding variables that ultimately compromise the validity of results, especially in establishing causation. Data on study characteristics, relief of fluid retention, dyspnea, weight change, diuresis, change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), change in serum creatinine, health status, subsequent heart failure (HF) events, and all-cause and cardiovascular death were abstracted.

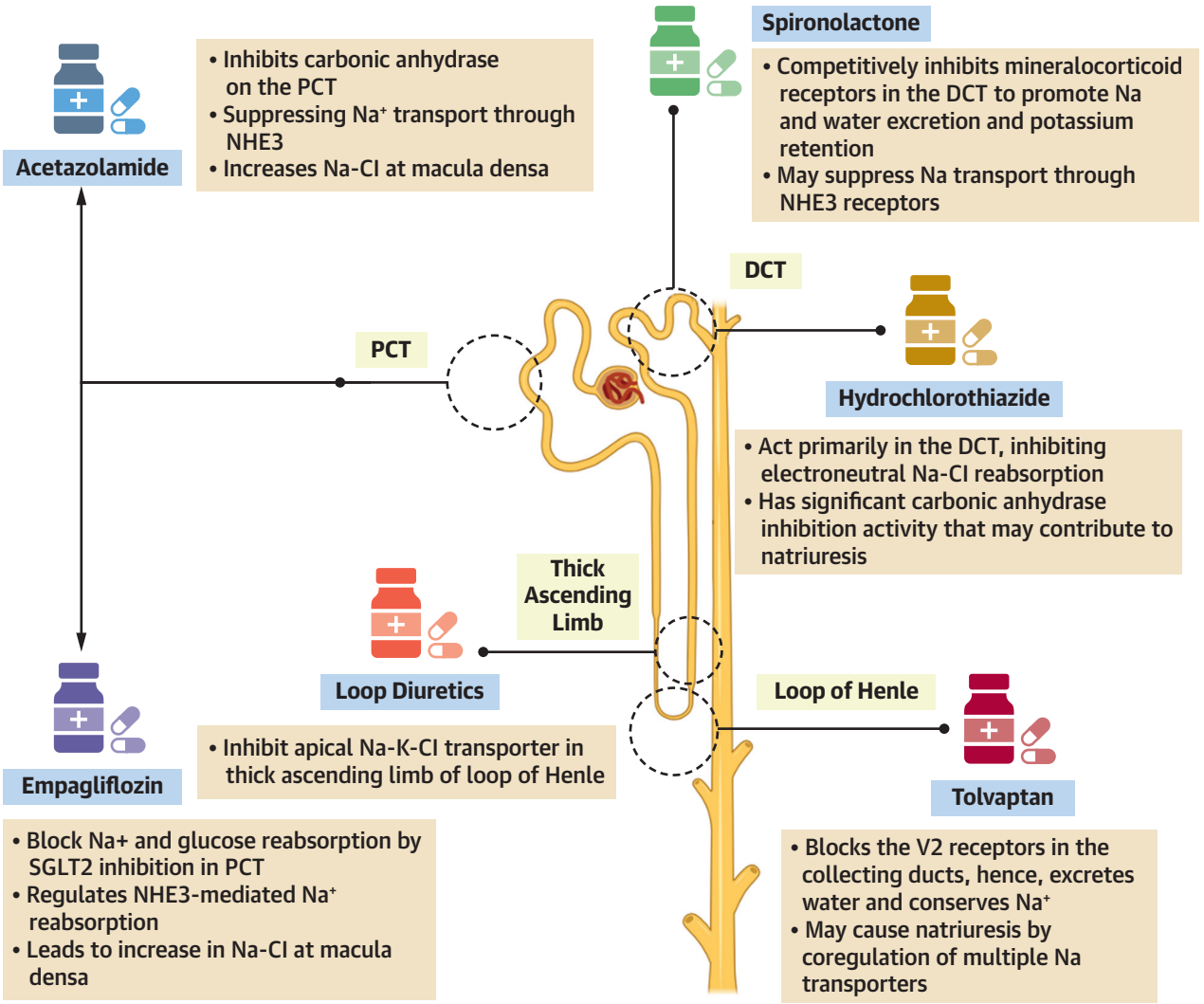
CLINICAL TRIALS. Twelve trials were included (**Table 1**).[8-19] These trials assessed dapagliflozin (DICTATE-AHF [Efficacy and Safety of Dapagliflozin in Acute Heart Failure]), acetazolamide (ADVOR [Acetazolamide in Decompensated Heart Failure with Volume Overload] and DIURESIS-CHF [Diamox/Aldactone to Increase the Urinary Excretion of Sodium: an Investigational Study in Congestive Heart Failure]), hydrochlorothiazide (CLOROTIC [Safety and Efficacy of the Combination of Loop With Thiazide-Type Diuretics in Patients With Decompensated Heart Failure]), empagliflozin (EMPULSE [Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized], EMPAG-HF [Empagliflozin in Acute Decompensated Hear Failure], and EMPA-RESPONSE-AHF [Randomized, Double Blind, Placebo Controlled, Multicenter Pilot Study on the Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure]), tolvaptan (TACTICS [Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure], SECRET of CHF [Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure], and EVEREST [Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan]), spironolactone (ATHENA-HF [Aldosterone Targeted Neurohormonal Combined With Natriuresis Therapy in Heart Failure], and dose/administration route of loop diuretic agents (DOSE [Diuretic Optimization Strategies Evaluation]) in patients with AHF. The follow-up period ranged from 0.4 to 40 weeks. All trials except DIURESIS-CHF were multicenter and double-blinded, as well as, except DOSE and ATHENA-HF, placebo-controlled.

MEASURES OF EFFICACY AND SAFETY. Most trials reported effects on relief of fluid retention or changes in dyspnea, urine output, weight or NT-proBNP. Relief of fluid retention was assessed with the use of varying criteria (**Table 2**). Dyspnea was measured by either Likert-type scale or visual analog scale (VAS) quantified as either change from baseline or area under the receiver-operating characteristic curve (AUC).[20,21] In trials where decongestion was assessed as only "relief of dyspnea," the results were

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 12, 2024; revised manuscript received August 29, 2024, accepted September 11, 2024.

CENTRAL ILLUSTRATION Mechanism of Diuretics Evaluated in Acute Heart Failure Trials


Spironolactone
• Competitively inhibits mineralocorticoid receptors in the DCT to promote Na and water excretion and potassium retention
• May suppress Na transport through NHE3 receptors
Acetazolamide
• Inhibits carbonic anhydrase on the PCT
• Suppressing Na+ transport through NHE3
• Increases Na-Cl at macula densa
DCT
PCT
Hydrochlorothiazide
• Act primarily in the DCT, inhibiting electroneutral Na-Cl reabsorption
• Has significant carbonic anhydrase inhibition activity that may contribute to natriuresis
Thick Ascending Limb
Loop Diuretics
Loop of Henle
Empagliflozin
• Inhibit apical Na-K-Cl transporter in thick ascending limb of loop of Henle
Tolvaptan
• Block Na+ and glucose reabsorption by SGLT2 inhibition in PCT
• Regulates NHE3-mediated Na+ reabsorption
• Leads to increase in Na-Cl at macula densa
• Blocks the V2 receptors in the collecting ducts, hence, excretes water and conserves Na+
• May cause natriuresis by coregulation of multiple Na transporters

Siddiqi TJ, et al. JACC Heart Fail. 2025;13(1):14–27.

The figure illustrates the site of action and mechanism for each diuretic discussed in the paper. In the proximal convoluted tubule (PCT), acetazolamide works primarily by inhibiting carbonic anhydrase, which in turn decreases H^+ production in the epithelial cells, leading to a decrease in H^+ secretion and Na^+ reabsorption via sodium-hydrogen exchanger 3 (NHE3). The suppression of NHE3, along with direct inhibition bicarbonate reabsorption, leads to sodium bicarbonate diuresis, with increased Na^+ reaching the macula densa. SGLT2is, such as empagliflozin, also target the PCT and work by inhibiting sodium and glucose reabsorption, causing glucosuria and natriuresis, leading to Na^+ increase in the macula densa, with regulatory effect on NHE3 as well. Loop diuretic agents act on the thick ascending limb (TAL) to inhibit Na-K-Cl transporter, resulting in natriuresis and potassium secretion. Spironolactone is a mineralocorticoid receptor antagonist at the DCT, leading to Na^+ and water excretion and K^+ retention, with further contribution to natriuresis through possible NHE3 suppression. Thiazide diuretic agents also act primarily on the distal convoluted tubules (DCT) to inhibit Na-Cl cotransporter, leading to salt excretion, which is also enhanced by underlying carbonic anhydrase inhibition by these drugs. Finally, tolvaptan acts on collecting ducts to inhibit vasopressin 2 (V2) receptors, leading to free water excretion. Moreover, there may be some sodium excretion due to concomitant activation of other sodium transporters in the loop of Henle. SGLT2i = sodium-glucose cotransporter 2 inhibitor.

presented under the dyspnea section. In trials where decongestion was defined as physical signs such as edema, pleural effusion, rales, and ascites, the results for decongestion were presented under the section "relief of fluid retention." Changes in dyspnea and weight were included if they occurred during the first 7 days of treatment. Health-related quality of life was measured by either the Kansas City Cardiomyopathy

Questionnaire (KCCQ), a 23-item patient led self-administered clinical outcomes assessment, or the EuroQol 5 Dimension (EQ-5D), which assess mobility, self-care, usual activities, pain/discomfort, and anxiety/depression as a reflection of health status. Kidney effects were assessed as between-group changes serum creatine from baseline.

RESULTS

PATIENT CHARACTERISTICS. The mean age in each trial was over 60 years, and patients were more often male, had NYHA functional class III-IV symptoms, elevated NT-proBNP levels, and a history of atrial fibrillation, hypertension, and diabetes. The average estimated glomerular filtration rate ranged from 39 to 115 mL/min/1.73 m^2. Most patients were taking loop diuretic agents at baseline, and loop diuretic agents were administered to all patients as part of background therapy or as the primary intervention.

WEIGHT. Nine trials reported changes in body weight. In DICTATE-AHF, dapagliflozin had no effect on weight at 5 days (−4.0 kg [Q1-Q3: −1.5 to −6.9 kg] vs −4.2 kg [Q1-Q3: −1.8 to −6.5 kg]; $P = 1.00$). In EMPA-RESPONSE-AHF and TACTICS, no significant effect was observed for empagliflozin and tolvaptan at 72 hours (−2.8 vs −2.3 kg [$P = 0.48$] and −8.2 vs −5.5 lb [$P = 0.07$], respectively). In ATHENA-HF, high-dose spironolactone had no significant effect on weight at 96 hours (−3.3 vs −2.8 kg; $P = 0.33$). In DOSE, no significant difference in weight was seen when diuretic agents were given as bolus vs continuous infusion (−6.8 vs −8.1 lbs; $P = 0.20$), but a significant difference was observed for high compared with low dose (−6.1 vs −8.7 lbs; $P = 0.001$) at 72 hours. In CLOROTIC and SECRET of CHF, hydrochlorothiazide (−2.3 vs −1.5 kg; $P = 0.002$), and tolvaptan (−3.54 vs −2.41 kg; $P = 0.006$) decreased weight at 72 hours vs placebo. In EVEREST, tolvaptan decreased weight at day 1 (−1.76 vs −0.97 kg; $P < 0.001$). In ADVOR, weight loss was reported at 36 hours but not after 3-4 days. Therefore, among the available trials, only the intensification of loop diuretic agents or the addition of a thiazide diuretic or a vasopressin antagonist was consistently accompanied by a decrease in body weight.

RELIEF OF FLUID RETENTION. Five trials reported results of changes in physical signs of fluid retention, although the definition of congestion varied greatly among trials. Between-group changes were reported at 96 hours in ATHENA-HF and at 72 hours in the other trials. ADVOR reported relief of fluid retention with acetazolamide compared with placebo ($P < 0.001$), but in DIURESIS-CHF, acetazolamide did not affect the relief of fluid retention at 72 hours (33% vs 31%; $P = 1.00$). In TACTICS, there was no benefit with tolvaptan (25% vs 16%; $P = 0.12$). In DOSE, no significant difference in relief of fluid retention was observed when diuretic agents were administered as bolus vs continuous infusion (14% vs 15%; $P = 0.78$) or low vs high dose (11% vs 18%; $P = 0.09$). In ATHENA-HF, there was no benefit with high-dose spironolactone for relief of fluid retention (−6 vs −6; $P = 0.41$) (Table 2).

DYSPNEA. Nine trials reported effects on dyspnea. In DICTATE-HF, dapagliflozin had no significant effect on ortho-edema score (OR: 0.65 [95% CI: 0.38-1.11]) at day 5. No differences were observed with hydrochlorothiazide, empagliflozin, and tolvaptan vs placebo on dyspnea in CHLOROTIC, EMPA-RESPONSE and TACTICS, respectively (AUC for VAS: 1,500 vs 1,320 at 96 hours [$P = 0.547$]; AUC for VAS: 1,264 vs 1,650 at 96 hours [$P = 0.18$]; and Likert-type scale: 69.2% vs 59.8% at 72 hours [$P = 0.16$]; respectively). In EMPULSE, empagliflozin improved dyspnea at day 15 (difference: −0.34 [Q1-Q3: −0.60 to 0.09]; $P = 0.008$); dyspnea was not assessed at earlier time points. In SECRET of CHF (Likert-type scale: 81.2% vs 66.3%2 at 72 hours; $P = 0.0$) and EVEREST (Likert-type scale: 74.3% vs 68.0% at 24 hours; $P < 0.01$), tolvaptan improved dyspnea. In ATHENA-HF, no benefit was reported with spironolactone on changes in Likert-type scale or VAS at 96 hours. In DOSE, no difference was observed with diuretic agents as a bolus or continuous infusion (AUC for VAS: 4,456 vs 4,699; $P = 0.36$), but high-dose strategy improved dyspnea compared with low-dose strategy (AUC for VAS: 4,478 vs 4,668 at 72 hours; $P = 0.04$). In ADVOR, acetazolamide did not significantly improve EQ-5D index (difference: −0.007 [Q1-Q3: −0.053 to 0.039]) and EQ-5D VAS (difference: −0.87 [Q1-Q3: −3.92 to 2.18]) at day 4. In EVEREST, tolvaptan had no effect on KCCQ overall summary score (OSS) at day 7 ($P = 0.39$). Thus, dyspnea appeared to be most consistently improved early in treatment with loop diuretic intensification and vasopressin antagonists.

NATRIURETIC PEPTIDES. In DICTATE-AHF, dapagliflozin had no effect on NT-proBNP at 30 days (median change from baseline: 42% vs 45%). Empagliflozin produced small decreases in NT-proBNP levels at day 5 in EMPAG-HF (difference: 0.89 pg/mL

TABLE 1 Study and Baseline Characteristics of AHF Trials

	DICTATE-AHF[8]	ADVOR[9]	CHLOROTIC[10]	EMPAG-HF[11]	EMPULSE[12]
Comparison	Dapagliflozin (n = 119) vs usual care (n = 119)	Acetazolamide (n = 259) vs placebo (n = 256)	HCTZ (n = 114) vs placebo (n = 116)	Empagliflozin (n = 29) vs placebo (n = 29)	Empagliflozin (n = 265) vs placebo (n = 265)
Primary endpoint	Cumulative weight change divided by cumulative loop diuretic dose	Decongestion	Change in weight; dyspnea response	Cumulative urine output	Composite of all-cause death, total HFE, time to first HFE or ≥5-point difference in KCCQ-TSS
Follow-up, wk	4	12	12	–	12
Age, y	65	78.2	83	74.7	70
Female	39.9	37.4	39.5	39.0	34.5
LVEF	40	43	55	44.5	31.5
NYHA functional class II	NA	12.7	35.65	13.6	35.1
NYHA functional class III	NA	57	50.9	55.9	52.6
NT-proBNP, pg/mL	2,642	6,042	114.96	4,773.7	3,202.5
Ischemia as cause of HF	49	NA	32.6	30.5	NA
Hypertension	NA	75	89.1	88.1	80.4
AF	42	72.4	68.7	45.8	49.4
DM	70	47.2	56.5	–	45.3
eGFR, mL/min/1.73 m^2	53	38.9	115.01	60.2	52
ACEI	52	52	55.2	72.9	33.4
ARB	–	–	–	–	21.9
ARNI	–	–	NA	16.9	15.3
MRA	51	41.6	35.2	18.6	52.1
BB	60	80.7	60.4	79.7	79.4
ICD	NA	15.2	NA	–	NA
CRT	NA	11.8	NA	–	NA

Values are %.

ACE = angiotensin-converting enzyme; ADVOR = Acetazolamide in Decompensated Heart Failure With Volume Overload; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; ATHENA-HF = Aldosterone Targeted Neurohormonal Combined With Natriuresis Therapy in Heart Failure; CLOROTIC = Safety and Efficacy of the Combination of Loop With Thiazide-type Diuretics in Patients With Decompensated Heart Failure; CRT = cardiac resynchronization therapy; CV = cardiovascular; DICTATE-AHF = Efficacy and Safety of Dapagliflozin in Acute Heart Failure; DOSE = Diuretic Optimization Strategies Evaluation; eGFR = estimated glomerular filtration rate; EMPA-RESPONSE-AHF = Randomized = Double Blind = Placebo Controlled = Multicenter Pilot Study on the Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure; EMPULSE = Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized; EVEREST = Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan; HHF = hospitalization for heart failure; HFE = heart failure event; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SECRET = Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure of CHF; TACTICS = Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure.

Continued on the next page

[Q1-Q3: 0.83-0.95 pg/mL]) and at day 30 in EMPULSE (adjusted geometric mean ratio: 0.90 [Q1-Q3: 0.82-0.98]). In EMPA-RESPONSE-AHF and ATHENA-HF, empagliflozin and high-dose spironolactone had no effect on NT-proBNP at 96 hours (−46% vs −42% [P = 0.63] and log values −0.55 vs −0.49 pg/mL [P = 0.57], respectively). In DIURESIS-CHF, acetazolamide had no effect on NT-proBNP at 72 hours (−12% ± 38% vs −9% ± 40%; P = 0.829). In DOSE, no difference in change in NT-proBNP was observed with low dose compared with high dose at 72 hours (−1,194 vs −1,882 pg/mL; P = 0.06). Similarly, no differences were observed for NT-proBNP change with bolus compared with continuous infusion at 72 hours (−1,316 vs −1,773 pg/mL; P = 0.44). Thus, in general, diuretic potentiation strategies did not report meaningful decreases in natriuretic peptides during the first week of treatment.

URINE OUTPUT. Eight of the 12 trials reported data on urine output. In ADVOR, acetazolamide produced an effect on diuresis at 48 hours (difference: 0.5 L [Q1-Q3: 0.2-0.8 L]). In CLOROTIC and ATHENA, hydrochlorothiazide and high-dose spironolactone had no effect on diuresis at 24 hours and 96 hours, respectively (1,775 vs 1,400 mL [P = 0.05] and 6,086 vs 5,584 mL [P = 0.57], respectively). In DICTATE-AHF, dapagliflozin had no effect on diuresis at 24 hours

TABLE 1 Continued

EMPA-RESPONSE-AHF[13]	DIURESIS-CHF[14]	TACTICS[15]	SECRET of CHF[16]	ATHENA-HF[17]	DOSE[18]	EVEREST[19]
Empagliflozin (n = 40) vs placebo (n = 39)	Acetazolamide (n = 180) vs placebo (n = 160)	Tolvaptan (n = 129) vs placebo (n = 128)	Tolvaptan (n = 122) vs placebo (n = 128)	High-dose spironolactone (n = 182) vs placebo (n = 178)	Bolus (n = 156) vs continuous (n = 152) furosemide; low dose (n = 151) vs high (n = 157) dose	Tolvaptan (n = 2,072) vs placebo (n = 2,061)
Dyspnea response; change in weight; change in NT-proBNP; hospital stay	Natriuresis	Dyspnea response	Dyspnea response	Change in NT-proBNP	Global assessment of symptoms	All-cause mortality; composite of CV death or HHF
9	0.4	–	4	–	8	40
76	80	64	68.5	65	66.2	65.9
33	35.0	33	32.5	35.8	26	26.6
36	43.0	33	34	32.5	35	27.5
NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	62	NA	NA	58.16
5,236	7,849	10,246	654.3	4,101.2	7,432.7	NA
28.5	NA	56	NA	62.8	57.14	64.7
62.1	NA	NA	NA	83.6	NA	70.9
71.1	NA	52	40.5	47.8	52.6	43.3
33.1	29.0	55	60	22.8	51.3	38.7
55	31.0	NA	47.5	56.5	NA	NA
43.5	41.0	61	56	60.3	63.96	84.2
4.01	–	–	–	–	–	–
–	NA	NA	NA	NA	NA	NA
46.5	59.0	NA	39	11.1	NA	NA
68	91.0	90	92	74.2	83.1	70.2
15.4	NA	47	43.5	16.1	38.6	NA
14	NA	13	23.5	NA	NA	NA

(median 3,026 vs 2,930 mL; $P = 0.49$). In EMPAG-HF and EMPA-RESPONSE-AHF, empagliflozin increased diuresis at 120 hours and 96 hours, respectively (differences: 2,125 mL [Q1-Q3: 840-3,550 mL] and 3,449 mL [Q1-Q3: 578-6,321 mL], respectively). In DOSE, no significant difference in diuresis was seen at 72 hours when diuretic agents were given as bolus vs continuous infusion (4,237 vs 4,249 mL; $P = 0.89$), but a significant difference was observed at 72 hours for high compared with low dose (3,575 vs 4,899 mL; $P > 0.01$). Thus, intensification of loop diuretic agents, acetazolamide, and SGLT2is produced between-group short-term difference on urine output.

NATRIURETIC RESPONSE. Four trials reported a natriuretic response. In ADVOR, acetazolamide increased natriuresis at 48 hours (468 ± 234 vs 369 ± 231 mmol). In DICTATE-AHF and DIURESIS-CHF, dapagliflozin and acetazolamide had no effect on natriuresis at 24 hours (244 mmol [Q1-Q3: 136-380 mmol] vs 272 mmol [Q1-Q3: 159-362 mmol] [$P = 0.81$] and 264 ± 126 vs 234 ± 133 mmol [$P = 0.515$], respectively). In CLOROTIC, hydrochlorothiazide had no effect on natriuresis at 96 hours (16.5 vs 14.5 mmol; $P = 0.842$). The information on natriuretic response is limited.

CHANGES IN CREATININE. Seven trials reported change in serum creatinine. In ADVOR, from baseline to 96 hours, acetazolamide was associated with a greater likelihood of an increase in creatinine >0.3 mg/dL (40.5% vs 18.9%; $P < 0.001$). In DIURESIS-CHF, serum creatine >0.3 mg/dL was seen more frequently in the acetazolamide group than in the placebo group at 72 hours (28% vs 0; $P = 0.046$). In CLOROTIC, increase in creatinine >26.5 μmol/L was seen more with hydrochlorothiazide at 96 hours (46.5% vs 17.2%; $P < 0.001$). In EMPAG-HF, increase in creatinine >26.5 μmol/L was seen numerically more often in the placebo group than in the empagliflozin group at day 5 (32.1% vs 11.5%), but that did not reach significance. In TACTICS, average serum creatinine changed by 0.03 and 0.06 mmol/L in tolvaptan vs placebo at 72 hours ($P = 0.55$). In SECRET of CHF, average creatinine increased from 1.66 to 1.80 mg/dL with

TABLE 2 Diuretic Strategies and Efficacy Outcomes in Acute Heart Failure Trials

Trial	Intervention and Control	Relief of Fluid Retention	
		Criteria	Finding
DICTATE-AHF[8]	Dapagliflozin (n = 119) vs usual care (n = 119)	–	–
ADVOR[9]	Acetazolamide (n = 259) vs placebo (n = 256)	Physical signs (absence of effusion, ascites, and edema)	Acetazolamide reduced relief of fluid retention at 72 h (42.2% vs 30.5%; RR: 1.46 [95% CI: 1.17-1.82])
CHLOROTIC[10]	HCTZ (n = 114) vs placebo (n = 116)	–	–
EMPAG-HF[11]	Empagliflozin (n = 29) vs placebo (n = 29)	–	–
EMPULSE[12]	Empagliflozin (n = 265) vs placebo (n = 265)	–	–
EMPA-RESPONSE-AHF[13]	Empagliflozin (n = 40) vs placebo (n = 39)	–	–
DIURESIS-CHF[14]	Acetazolamide (n = 180) vs placebo (n = 160)	Physical signs (absence of elevated jugular venous pressure, hepatosplenomegaly, ascites, trace edema, or rales)	Acetazolamide had no significant effect on relief of fluid retention at 72 h (33% vs 31%; $P = 1.00$)
TACTICS[15]	Tolvaptan (n = 129) vs placebo (n = 128)	Physical signs (jugular venous pressure <8 cm, no orthopnea, and trace or less peripheral edema)	Tolvaptan had no significant effect on relief of fluid retention at 72 h (25% vs 16%; $P = 0.12$)
SECRET of CHF[16]	Tolvaptan (n = 122) vs placebo (n = 128)	–	–
ATHENA-HF[17]	High-dose spironolactone (n = 182) vs placebo (n = 178)	Physical signs (absence of orthopnea, jugular venous distention, and pedal edema)	High-dose spironolactone had no significant effect on relief of fluid retention at 96 h (congestion score −6 vs −6; $P = 0.41$)
DOSE (low-dose vs high-dose therapy)[18]	Low dose (n = 151) vs high dose (n = 157)	Physical signs (jugular venous pressure <8 cm, no orthopnea, and trace or less peripheral edema)	No significant difference in relief of fluid retention with low-dose compared with high-dose at 72 h (11% vs 18%; $P = 0.09$)
DOSE (bolus vs continuous infusion)[18]	Bolus (n = 156) vs continuous (n = 152) furosemide		No significant difference in relief of fluid retention with bolus compared with continuous infusion at 72 h (14% vs 15%; $P = 0.78$)
EVEREST[19]	Tolvaptan (n = 2,072) vs placebo (n = 2,061)	–	–

aGMR = adjusted geometric mean ratio; HCTZ = hydrochlorothiazide; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Table 1.

Continued on the next page

TABLE 2 Continued

Dyspnea		Change in Weight	Change in NT-ProBNP	Diuresis
Criteria	Finding	Finding	Finding	Finding
Symptoms (blinded congestion scores)	Dapagliflozin had better odds of improved edema score (OR: 0.44 [95% CI: 0.20-0.97]) but had no significant effect on ortho-edema score at 5 d (OR: 0.65 [95% CI: 0.38-1.11])	Dapagliflozin had no significant effect on weight change at 5 d (−4.0 kg [Q1-Q3: −1.5 to −6.9] vs −4.2 kg [Q1-Q3: −1.8 to −6.5 kg]; $P = 1.00$)	Dapagliflozin had no significant effect on NT-proBNP at 30 d (median change from baseline: 42% vs 45%)	Dapagliflozin had no significant effect on diuresis at 24 h (median: 3,026 vs 2,930 mL; $P = 0.49$)
–	–	–	–	Acetazolamide increased diuresis at 48 h (difference: 0.5 L [Q1-Q3: 0.2-0.8 L])
VAS quantified as the AUC of serial assessments	HCTZ had no significant effect on dyspnea response at 96 h (AUC: 1,500 vs 1,320; $P = 0.547$)	HCTZ reduced weight at 72 h (−2.3 vs −1.5 kg; $P = 0.002$)	–	HCTZ had no significant effect on diuresis at 24 h (1,775 vs 1,400 mL; $P = 0.05$)
–	–	Empagliflozin had no significant effect on weight change at 120 h (difference: −1.2 kg [Q1-Q3: −2.99 to 0.63 kg])	Empagliflozin reduced NT-proBNP levels at 120 h (0.89 [Q1-Q3: 0.83-0.95])	Empagliflozin increased diuresis at 120 h (difference: 2,125 mL [Q1-Q3: 840-3,550 mL])
Symptoms (absence of dyspnea, orthopnea, fatigue)	Empagliflozin improved dyspnea at 15 d (difference: −0.34 [Q1-Q3: −0.60 to 0.09]; $P = 0.008$)	Empagliflozin reduced weight at 30 d (−2.79 [Q1-Q3: −5.03 to −0.54])	Empagliflozin reduced NT-proBNP at 30 d (aGMR: 0.90 [95% CI: 0.82-0.98])	–
VAS quantified as the AUC of serial assessments	Empagliflozin had no significant effect on dyspnea response at 96 h (AUC: 1,264 vs 1,650; $P = 0.18$)	Empagliflozin had no significant effect on weight change at 96 h (−2.8 vs −2.3 kg; $P = 0.48$)	Empagliflozin had no significant effect on NT-proBNP at 96 h (change: −46% vs −42%; $P = 0.63$)	Empagliflozin increased diuresis at 96 h (difference: 3,449 mL [Q1-Q3: 578-6,321 mL])
–	–	–	Acetazolamide had no significant effect on NT-proBNP at 72 h (−12 ± 38% vs −9 ± 40%; $P = 0.829$)	Acetazolamide had no significant effect on diuresis at 24 h (264 ± 126 mmol vs 234 ± 133 mmol; $P = 0.515$)
Proportion of patients with at least moderate improvement in dyspnea by 7-point Likert scale	Tolvaptan had no significant effect on dyspnea response at 72 h (69.2% vs 59.8%; $P = 0.16$)	Tolvaptan had no significant effect on weight change at 72 h (−8.2 vs −5.5 lb; $P = 0.07$)	–	–
Proportion of patients with improvements in dyspnea by 7-point Likert scale	Tolvaptan improved dyspnea at 72 h (81.2% vs 66.3%; $P = 0.02$)	Tolvaptan reduced weight at 72 h (−3.54 vs −2.41 kg; $P = 0.006$)	–	–
Improvements in dyspnea by 7-point Likert scale VAS of serial assessments	High-dose spironolactone had no significant effect on dyspnea at 96 h (2 vs 2; $P = 0.31$) High-dose spironolactone had no significant effect on dyspnea at 96 h (15 vs 15; $P = 0.61$)	High-dose spironolactone had no significant effect on weight at 96 h (−3.3 vs −2.8 kg; $P = 0.33$)	High-dose spironolactone had no significant effect on change in NT-proBNP at 96 h (log values: −0.55 vs −0.49; $P = 0.57$)	High-dose spironolactone had no significant effect on diuresis at 96 h (6,086 vs 5,584 mL; $P = 0.57$)
VAS quantified as the AUC of serial assessments	Difference in dyspnea response with high-dose compared with low-dose at 72 h (AUC: 4,668 vs 4,478; $P = 0.04$)	Difference in weight change with low dose compared with high dose at 72 h (−6.1 vs −8.7 lb; $P = 0.01$)	No significant difference in change in NT-proBNP with low-dose compared with high-dose at 72 h (−1,194 vs −1,882 pg/mL; $P = 0.06$)	Difference in diuresis with low dose compared with high dose at 72 h (3,575 vs 4,899 mL; $P > 0.01$)
	No significant difference in dyspnea response with bolus compared with continuous infusion at 72 h (AUC: 4,456 vs 4,699; $P = 0.36$)	No significant weight change was observed for bolus compared with continuous infusion at 72 h (−6.8 ± 7.8 lb vs −8.1 ± 10.3 lb; $P = 0.20$)	No significant difference in change in NT-proBNP with bolus compared with continuous infusion at 72 h (−1,316 vs −1,773 pg/mL; $P = 0.44$)	No significant difference in diuresis for bolus compared with continuous infusion (4,237 vs 4,249 mL; $P = 0.89$)
Proportion of patients with improvements in dyspnea by 7-point Likert scale	Tolvaptan improved dyspnea compared with placebo at 24 h (74.3% vs 68.0%; $P < 0.01$)	Tolvaptan decreased weight compared with placebo at 1 d (−1.76 vs −0.97 kg; $P < 0.001$)	–	–

tolvaptan and from 1.68 to 1.82 mg/dL with placebo at day 7 ($P = 0.66$). In EVEREST, there was a difference in increase in creatine at day 7 in the tolvaptan groups (0.08 vs 0.03 mg/dL; $P < 0.01$) (Table 3). In ATHENA-HF, >0.3 mg/dL increase in creatine occurred in 28% of patients with spironolactone and 32% of patients with placebo ($P = 0.64$). In DOSE, >0.3 mg/dL increase in creatine occurred in 17.5% of those with bolus and 19% of those with continuous infusion ($P = 0.64$). A higher proportion increased >0.3 mg/dL in high- vs low-dose strategy at 72 hours (23% vs 14%; $P = 0.04$). Thus, all diuretic strategies were accompanied by short-term increases in serum creatinine.

CARDIOVASCULAR OUTCOMES. Cardiovascular outcomes are summarized in Table 4. In DICTATE-AHF, the rate of worsening HF or all-cause mortality was similar in the dapagliflozin and usual care arm over a 4 week follow-up period. During a follow-up of 12 weeks, no benefit was seen in either the ADVOR or the CLOROTIC trial with numerically higher proportion of patients suffering adverse outcomes with both acetazolamide and with hydrochlorothiazide. In SECRETS of CHF the follow-up period was 4 weeks and the composite outcome of cardiovascular death or hospitalization for HF and all-cause death occurred in 11.8% and 5.0% patients in the tolvaptan group and 12.8% and 4.8% patients in the placebo group, respectively. However, tolvaptan did not improve major cardiovascular outcomes when maintained for an average of 40 weeks. Over a 12-week follow-up period, cardiovascular deaths and HF events (12.8% vs 18.5%; HR: 0.69 [95% CI: 0.45-1.06]) were numerically less frequent with empagliflozin. In EMPA-RESPONSE-AHF, there were fewer occurrences of all-cause death, hospitalization for HF, or worsening HF (10.0% vs 33.3%; $P = 0.014$) and of hospitalization for HF or worsening HF (7.5% vs 25.6%; $P = 0.037$) in the empagliflozin arm compared with placebo over a follow-up period of 9 weeks, but the number of events was small. In ATHENA-HF, there was no difference in hospitalization for HF, emergency department visit, or death between the high-dose spironolactone and placebo groups (HR: 1.22 [Q1-Q3: 0.68-2.19]). In DOSE, the follow-up was 8 weeks, and low- compared with higher-dose diuretic agents (HR: 0.83 [95% CI: 0.60-1.15]) or bolus vs continuous infusion (HR: 1.15 [95% CI: 0.83-1.59]) of loop diuretic agents did not lower risk of all-cause death, hospitalization, or emergency department visit. Thus, short-term diuretic potentiation strategies have not produced a consistent improvement in cardiovascular outcomes.

DISCUSSION

In trials investigating the impact of diuretic strategies on patients with AHF, we highlight several key findings (Central Illustration). First, a notable reduction in body weight and an improvement in dyspnea were reported only with the intensification of loop diuretic agents or the addition of a vasopressin antagonist. The addition of a thiazide diuretic or a vasopressin antagonist resulted in a decrease in body weight at the end of the treatment period. Second, most diuretic potentiation strategies have not been consistently accompanied by relief from signs of fluid retention or a meaningful decrease in natriuretic peptide during the first 3-7 days of treatment. Third, SGLT2is, acetazolamide, and intensification of loop diuretic agents led to meaningful increases in urine output during the first week of treatment. Fourth, all diuretic strategies were associated with short-term increases in serum creatinine. Finally, short-term diuretic potentiation strategies have not produced an improvement in cardiovascular outcomes.

Change in weight was one of the most commonly reported outcomes. Such data are challenging to obtain and may be prone to measurement error for many reasons (eg, variation in scales, patient clothing, time of day for measurement).[22] There may also be confounding if the drug also produces glycosuria and thus caloric loss. Among trials that reported weight changes, CLOROTIC, SECRET of CHF, EVEREST, ADVOR, and DOSE reported a short-term decrease in body weight. In a combined analysis of DOSE, ROSE (The Renal Optimization Strategies Evaluation), and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), weight loss during the initial 72 to 96 hours correlated with relief in congestion but did not show a significant association with the combined primary outcome of death, rehospitalization, or unplanned hospital visits within the subsequent 60 days.[24] However, weight reduction observed in AHF trials did not translate into observed improved clinical outcomes after discharge (ie, rehospitalization and death), although all trials (except EVEREST) were underpowered for this question.[23]

Observational data indicate that congestion at discharge serves to identify patients with unfavorable postdischarge outcomes, but this finding does not imply that more intense decongestion would improve

TABLE 3 Diuretic Strategies and Safety Outcomes in Acute Heart Failure Trials

Trial	Change in Creatinine	Change in eGFR
DICTATE-AHF[8]	–	No difference was observed for change in eGFR between the dapagliflozin and usually care group (−2 vs −3 mL/min/1.73 m^2)
ADVOR[9]	Doubling of serum creatinine in 0.8% of patients in acetazolamide group and in no patients in the placebo group ($P = 0.24$)	≥50% reduction in eGFR occurred in 1.6% of patients in acetazolamide group and 0.4% of patients in placebo group ($P = 0.21$)
	From baseline to 96 h, acetazolamide was associated with a higher incidence rise in creatinine >0.3 mg/dL (40.5% vs 18.9%; $P < 0.001$)	From baseline to 96 h, average eGFR decreased from 40 to 35 mL/min/m^3 in acetazolamide group and increased from 38 to 39 mL/min/m^3 in placebo group
CHLOROTIC[10]	Serum creatinine >26.5 μmol/L in 46.5% of patients in hydrochlorothiazide group vs 17.2% of patients in placebo group ($P < 0.001$)	≥50% reduction in eGFR occurred in equal number of patients in hydrochlorothiazide and placebo groups (0.9% vs 0.9%; $P = 1.00$)
EMPAG-HF[11]	Serum creatinine ≥26.5 μmol/L in 11.5% of patients in empagliflozin group and 32.1% of patients in the placebo group at 5 d	No differences in changes in eGFR between the 2 groups (51 ± 19 vs 54 ± 17 mL/min/1.73 m^2; $P = 598$) at 5 d
EMPULSE[12]	–	Empagliflozin caused an initial decline in eGFR, reaching a difference of 2 mL/min/1.73 m^2 at 15 d compared with placebo ($P = 0.0822$)
EMPA-RESPONSE-AHF[13]	–	During the first 72 h, empagliflozin caused a significant decrease in eGFR (−10 ± 12 vs −2 ± 12 mL/min/1.73 m^2) compared with placebo ($P = 0.009$)
DIURESIS-CHF[14]	Serum creatine >0.3 mg/dL in 28% of acetazolamide group vs none in placebo group at 72 h ($P = 0.046$).	–
TACTICS[15]	Serum creatine >0.3 mg/dL was significantly more frequent in the tolvaptan group	–
	From baseline to 72 h, average serum creatinine changed by 0.03 and 0.06 mmol/L in the tolvaptan and placebo groups, respectively ($P = 0.55$)	–
SECRET of CHF[16]	From baseline to 7 d, average serum creatinine increased from 1.66 to 1.80 mg/dL in the tolvaptan group and from 1.68 to 1.82 mL/min/m^3 in the placebo group ($P = 0.66$)	eGFR decreased from 47.8 to 44.2 mL/min/m^3 in the tolvaptan group and from 47.4 to 44.9 mL/min/m^3 in the placebo group ($P = 0.66$)
ATHENA-HF[17]	>0.3 mg/dL increase in serum creatine occurred in 28% of patients in the high-dose spironolactone group and in 32% of the control group ($P = 0.42$)	From baseline to 96 h, average serum eGFR decreased by −4.13 and −5.56 mL/min/1.73 m^2 in the high-dose spironolactone and control groups, respectively ($P = 0.155$)
	From baseline to 96 h, average serum creatine increased by 0.15 and 0.16 mg/dL in the high-dose spironolactone and control groups, respectively ($P = 0.155$)	
DOSE (low-dose vs high-dose therapy)[18]	A higher proportion of >0.3 mg/dL increase in serum creatine occurred in the high- compared with low-dose strategy (23% vs 14%; $P = 0.04$)	–
DOSE (bolus vs continuous infusion)[18]	>0.3 mg/dL increase in serum creatine occurred in 17.5% of patients in the bolus group and in 19% of the continuous infusion group ($P = 0.64$)	–
EVEREST[19]	Significant difference in the increase in serum creatine from baseline to 7 d in the tolvaptan and placebo groups (0.08 vs 0.03 mg/dL; $P < 0.01$)	–

eGFR = estimated glomerular filtration rate; other abbreviations as in Table 1.

outcomes.[21] Ease of diuresis per se is a likely indicator of prognosis independently from whether diuresis is achieved. It is noteworthy that clinical congestion was assessed by symptoms in some trials and by physical signs in others. For example, in EMPULSE, decongestion was evaluated based on symptoms at a 90-day follow-up, whereas in ADVOR, acetazolamide was evaluated by physical signs at 36 hours. To complicate matters further, DICTATE-AHF was open label, and in ADVOR, investigators were not blinded to changes in serum bicarbonate, potentially introducing bias in the assessment of physical signs and congestion.

Like the assessment of decongestion, the evaluation of dyspnea response varied across trials, using tools such as a Likert-type scale or VAS. Among trials reporting dyspnea response, DICTATE-AHF, SECRET of CHF, EVEREST, and DOSE indicate that tolvaptan and high-dose loop diuretic agents led to a reduction in dyspnea for patients with AHF. It is noteworthy that patient-assessed dyspnea exhibits only a modest correlation with physician-assessed changes in HF signs, such as edema or jugular venous distension.[25]

The prevalence of diuretic resistance in patients with AHF is 20% to 30%, and it leads to a worse

TABLE 4 Diuretic Strategies and Cardiovascular (CV) Outcomes In Acute Heart Failure Trials

Trial Name	Outcome	Intervention			Control			HR, RR, or OR (95% CI)
		n	N	%	n	N	%	
DICTATE-AHF[8]	WHF	4	119	3.4	3	119	2.5	
	All-cause death	20	119	16.8	19	119	16.0	
ADVOR[9]	All-cause death or HHF	76	256	29.7	72	259	27.8	1.07 (0.78-1.47)
	All-cause death	39	256	15.2	31	259	12	1.28 (0.78-2.10)
	HHF	47	256	18.4	45	259	17.4	1.07 (0.71-1.61)
CHLOROTIC[10]	All-cause death	23	114	20.2	19	116	16.4	
	All-cause hospitalization	43	114	37.7	40	116	34.5	
EMPULSE[12]	All-cause death	11	265	4.2	22	265	8.3	
	HF events	28	265	10.6	39	265	14.7	
	CV death or HF event	34	265	12.8	49	265	18.5	0.69 (0.45-1.06)
	HHF	14	265	5.3	12	265	4.5	1.18 (0.53-2.60)
EMPA-RESPONSE-AHF[13]	All-cause death, HHF, or WHF	4	40	10	13	39	33.3	
	WHF	1	40	2.5	5	39	12.8	
	HHF	2	40	5	5	39	12.8	
	All-cause death	1	40	2.5	1	39	2.6	
	HHF or WHF	3	40	7.5	10	39	25.6	
	All-cause death or HHF	3	40	7.5	8	39	20.5	
TACTICS[15]	All-cause death or hospitalization	33	129	25.6	29	128	22.6	
	All-cause death	6	129	4.65	6	128	4.68	
SECRET of CHF[16]	CV death or HHF	14	122	11.8	16	128	12.8	
	All-cause death	6	122	5	6	128	4.8	
ATHENA-HF[17]	HHF, ED visit, or death		182			178		1.22 (0.68-2.19)
	Inpatient WHF	33	182	19	31	178	18	
	Outpatient WHF	19	182	11	17	178	10	
DOSE (low-dose vs high-dose therapy)[18]	All-cause death, rehospitalization or ED visit	63	156	42.9	67	152	41.4	1.15 (0.83-1.59)
	All-cause death	13	156	8	16	152	11	
	Rehospitalization	50	156	33	42	152	29	
	ED visit	16	156	11	21	152	15	
DOSE (bolus vs continuous infusion)[18]	All-cause death, rehospitalization, or ED visit	67	151	41.7	63	157	42.6	0.83 (0.60-1.15)
	All-cause death	14	151	11	15	157	14	
	Rehospitalization	51	151	36	41	157	27	
	ED visit	16	151	11	21	157	14	
EVEREST[19]	All-cause mortality	537	2,072	25.9	543	2,061	26.3	0.98 (0.87-1.11)
	CV death or HF hospitalizations	871	2,072	42	829	2,061	40.2	1.04 (0.95-1.14)
	CV death or hospitalizations	1,006	2,072	48.5	958	2,061	46.4	1.04 (0.95-1.14)
	CV death	421	2,072	20.3	408	2,061	19.8	
	HF events	757	2,072	36.5	739	2,061	35.6	

ED = emergency department; HF = heart failure; HHF = hospitalization for heart failure; WHF = worsening heart failure; other abbreviations as in Table 1.

prognosis due to persistent fluid retention or failure to relieve symptoms despite receiving standard or high doses of diuretics. In CLOROTIC, the addition of hydrochlorothiazide improved loop diuretic response in AHF patients with diuretic resistance. In addition, tolvaptan improved dyspnea and reduced weight at 72 hours in the SECRET of CHF trial, which included AHF patients with diuretic resistance, kidney impairment, and hyponatremia. Of note, most of the trials did not provide data on diuretic resistance.

Previous evidence supports the use of SGLT2is in ambulatory patients with HF with reduced and preserved ejection fractions.[26-28] Findings from EMPULSE complement those findings by focusing on patients hospitalized for AHF across the range of ejection fractions. In the current review, SOLOIST-WHF (Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) was not included in the present review, because participants received drug therapy after the first 3 days and only 50% received the drug before discharge.[29]

Other foundational HF drugs also may benefit patients with AHF. In STRONG-HF (The Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-ProBNP Testing, of Heart Failure Therapies), 1,078 patients with AHF were randomized to either usual care or high-intensity care.[30] High-intensity

care, with higher up-titration of guideline-recommended therapies, was associated with a reduction in congestion and associated symptoms. Similarly, in PIONEER-HF (Comparison of Sacubitril-Valsartan Versus Enalapril on Effect on NT-ProBNP in Patients Stabilized From an Acute Heart Failure Episode), a greater reduction in NT-proBNP was observed with sacubitril/valsartan than with enalapril, which was evident as early as week 1 (ratio of change: 0.76 [95% CI: 0.69-0.85]), and hospitalization for HF during the subsequent 8 weeks was less frequent in the sacubitril/valsartan group than in the enalapril group.[31]

Worsening renal function is associated with reduced survival independently from left ventricular function and severity of HF;[32] however, isolated changes in creatine that occur during decongestion do not necessarily translate to adverse outcomes and, in patients who undergo diuresis, may portend better prognosis.[33] In the trials in the current analysis, we observed an increase in serum creatine in response to all diuretic potentiation strategies.

Two trials of diuretic agents in patients with AHF were not included in the present review. In TRANSFORM-HF (Torsemide Comparison With Furosemide for Management of Heart Failure), no difference was observed in the risk for all-cause mortality over 12 months between the loop diuretic strategies of torsemide and furosemide in patients with AHF.[34] Although TRANSFORM-HF studied the effects of diuretic therapy in patients with AHF, it did not assess in-hospital outcomes, which was also true for EMPULSE. PUSH-AHF (Pragmatic Urinary Sodium-Based Treatment Algorithm in Acute Heart Failure) randomized 301 AHF patients to either natriuresis-guided diuretic therapy or standard care. Because of the focus on natriuresis-guided therapy (rather the use of a specific agent), this trial was excluded from this review. It is notable, however, that this approach increased diuresis at 24 hours without affecting all-cause mortality or HF hospitalization.[35]

The current evidence identifies several gaps in the field of diuretic potentiation therapy for AHF that require attention for future investigations. Despite large and expensive clinical trials being conducted to evaluate the efficacy of diuretic intensification in AHF, the findings do not provide consistent evidence of benefit. Moreover, with a paucity of head to head comparison between drugs, it is difficult to determine benefits of one diuretic over another. Another notable gap pertains to the suboptimal methods used to measure outcomes in AHF trials, with a lack of consensus regarding optimal determination of congestion, utility of congestion scores, and the role of lung ultrasound for assessing congestion. To address these gaps effectively, well designed prospective studies and standardized assessment protocols may provide helpful bases to allow comparison and aid clinical decision making. Such initiatives are important for advancing our understanding of AHF pathophysiology, refining treatment strategies, and ultimately enhancing patient outcomes.

CONCLUSIONS

Current evidence suggests that all diuretic strategies have the potential to produce diuresis, but are accompanied by acute increases in serum creatinine. The importance of short-term decongestion for long-term outcomes has not been established.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Packer has received consulting fees from 89bio, Abbvie, Altimmune, Amgen, Ardelyx, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Lilly, Moderna, Novartis, Reata, Regeneron, Relypsa, and Salamandra, and is a Trial Executive Committee member of the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. Dr Ezekowitz has received research grants from American Regent, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb/Pfizer, eko.ai, US2.ai, Merck, Novartis, Otsuka, Sanofi, and Servier, and consulting fees from American Regent, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb/Pfizer, Merck, Novartis, Otsuka, Sanofi, and Servier. Dr Fonarow has served as a consultant for Abbott, Amgen, AstraZeneca, Bayer, Cytokinetics, Eli Lilly, Johnson and Johnson, Medtronic, Merck, Novartis, and Pfizer. Dr Greene has received research support from the Duke University Department of Medicine Chair's Research Award, American Heart Association, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Cytokinetics, Merck, Novartis, Otsuka, Pfizer, and Sanofi; has served on advisory boards or as a consultant for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Corteria Pharmaceuticals, CSL Vifor, Cytokinetics, Eli Lilly, Lexicon, Merck, Novo Nordisk, Otsuka, Roche Diagnostics, Sanofi, scPharmaceuticals, Tricog Health, and Urovant Pharmaceuticals; and has received speaker fees from Bayer, Boehringer Ingelheim, Cytokinetics, Lexicon, and Roche Diagnostics. Dr Mentz has received research support and honoraria from Abbott, American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim/Eli Lilly, Boston Scientific, Cytokinetics, Fast BioMedical, Gilead, Innolife, Medtronic, Merck, Novartis, Relypsa, Respicardia, Roche, Sanofi, Vifor, Windtree Therapeutics, and Zoll. Dr Testani has received fees from 3ive labs, Bayer, Bristol-Myers Squibb, AstraZeneca, Novartis, Cardionomic, MagentaMed, Reprieve, Fire1, W.L. Gore and Associates, Sanofi, Sequana Medical, Otsuka, Abbott, Merck, Windtree Therapeutics, Lexicon Pharmaceuticals, Precardia, Relypsa, Regeneron, Becton Dickinson, Edwards Lifesciences, and Lilly, and holds a patent for treatment of diuretic resistance issued to Yale and Corvidia Therapeutics, a patent for methods for measuring renalase issued to Yale, and a patent for treatment of diuretic resistance pending with Reprieve. Dr Voors has received research support and/or has been a consultant for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Merck, Myokardia, Novo Nordisk, Novartis, and Roche Diagnostics. Dr Butler has received payment or honoraria for lectures, presentations, Speakers Bureau, manuscript writing, or educational events from Abbott, Adrenomed, Amgen,

Applied Therapeutics, Array, AstraZeneca, Bayer, BerlinCures, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, Sequana Medical, Occlutech, and Vifor, and is a Trial Executive Committee member of Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance. All other authors have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Prof Javed Butler, Baylor Scott and White Research Institute, Baylor Scott and White Research Institute, 3434 Live Oak Street, Suite 501, Dallas, Texas 75204, USA. E-mail: javed.butler@bswhealth.org. X handle: @JavedButler1.

REFERENCES

1. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 2012;5:54–62.

2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

3. Arrigo M, Jessup M, Mullens W, et al. Acute heart failure. *Nat Rev Dis Primers*. 2020;6:16.

4. Dharmarajan K, Hsieh AF, Lin Z, et al. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *JAMA*. 2013;309:355–363.

5. Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. *JAMA*. 2010;303:2141–2147.

6. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA*. 2013;310:2533–2543.

7. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367:2296–2304.

8. Cox ZL, Collins SP, Aaron M, et al. Efficacy and safety of dapagliflozin in acute heart failure: rationale and design of the DICTATE-AHF trial. *Am Heart J*. 2021;232:116–124.

9. Mullens W, Dauw J, Martens P, et al, ADVOR Study Group. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*. 2022;387(13):1185–1195.

10. Trullàs JC, Morales-Rull JL, Casado J, et al, CLOROTIC Trial Investigators. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J*. 2023;44(5):411–421.

11. Schulze PC, Bogoviku J, Westphal J, et al. Effects of early empagliflozin initiation on diuresis and kidney function in patients with acute decompensated heart failure (EMPAG-HF). *Circulation*. 2022;146(4):289–298.

12. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28(3):568–574.

13. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail*. 2020;22(4):713–722.

14. Felker GM, Lee KL, Bull DA, et al, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797–805.

15. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol*. 2017;69(11):1399–1406.

16. Konstam MA, Kiernan M, Chandler A, et al, SECRET of CHF Investigators, Coordinators, and Committee Members. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol*. 2017;69(11):1409–1419.

17. Butler J, Anstrom KJ, Felker GM, et al, National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol*. 2017;2(9):950–958.

18. Felker GM, Lee KL, Bull DA, et al, NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797–805.

19. Konstam MA, Gheorghiade M, Burnett JC Jr, et al, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297(12):1319–1331.

20. Weber CK, Miglioranza MH, Moraes MA, et al. The five-point Likert scale for dyspnea can properly assess the degree of pulmonary congestion and predict adverse events in heart failure outpatients. *Clinics (Sao Paulo)*. 2014;69(5):341–346.

21. Mishra EK, Corcoran JP, Hallifax RJ, Stradling J, Maskell NA, Rahman NM. Defining the minimal important difference for the visual analogue scale assessing dyspnea in patients with malignant pleural effusions. *PLoS One*. 2015;10(4):e0123798.

22. Testani JM, Brisco MA, et al. Substantial discrepancy between fluid and weight loss during acute decompensated heart failure treatment. *Am J Med*. 2015;128(7):776–783.e4.

23. Ambrosy AP, Pang PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J*. 2013;34:835–843.

24. Groarke JD, Stevens SR, Mentz RJ, et al. Clinical significance of early fluid and weight change during acute heart failure hospitalization. *J Card Fail*. 2018;24:542–549.

25. Smithline HA, Caglar S, Blank FS. Physician vs patient assessment of dyspnea during acute decompensated heart failure. *Congest Heart Fail*. 2010;16(2):60–64.

26. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.

27. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

28. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461.

29. Bhatt DL, Szarek M, Steg PG, et al, SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384(2):117–128.

30. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022;400(10367):1938–1952.

31. Velazquez EJ, Morrow DA, DeVore AD, et al, PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380(6):539–548.

32. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35:455–469.

33. Emmens JE, ter Maaten JM, Matsue Y, et al. Worsening renal function in acute heart failure in

the context of diuretic response. *Eur J Heart Fail*. 2022;24(2):365–374.

34. Mentz RJ, Anstrom KJ, Eisenstein EL, et al, TRANSFORM-HF Investigators. Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: the TRANSFORM-HF randomized clinical trial. *JAMA*. 2023;329(3):214–223.

35. Ter Maaten JM, Beldhuis IE, van der Meer P, Krikken JA, et al. Natriuresis-guided diuretic therapy in acute heart failure: a pragmatic randomized trial. *Nat Med*. 2023;29(10):2625–2632.

KEY WORDS acute heart failure, clinical trials, diuretic agents

APPENDIX For a supplemental table, please see the online version of this paper.